Suspension Polymerization of L-Lactide in Supercritical Carbon Dioxide in the Presence of a Triblock Copolymer Stabilizer

Daniel Bratton,[†] Malcolm Brown,[‡] and Steven M. Howdle*,[†]

School of Chemistry, University of Nottingham, Nottingham, England, NG7 2RD, and Smith & Nephew Group Research Centre, York Science Park, Heslington, York, England, YO10 5DF

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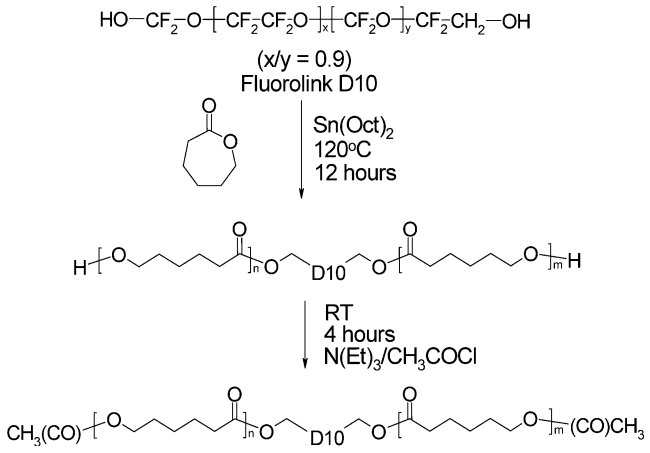
Introduction. Supercritical carbon dioxide ($scCO_2$) has attracted much attention in recent years as a replacement for traditional organic solvents.[1,2] The key attractions in the use of $scCO_2$ are the lack of toxic solvent residues in the product and ease of product recovery by simply venting the reaction vessel. It has been shown by many groups that the addition of a suitable stabilizer to free radical polymerizations conducted in $scCO_2$ facilitates the synthesis of high molecular weight polymers of well-defined morphology, for example, as microparticles or latexes.[3] Stabilizers used in $scCO_2$ typically contain a segment exhibiting high solubility in $scCO_2$, such as a fluorinated section ("CO_2-philic"),[3] together with a second portion designed to interact with the growing polymer chain, for example a short section of $scCO_2$ insoluble polymer or a headgroup which specifically interacts with the growing polymer in question ("polymer-philic"). A wide variety of stabilizer architectures effective for free radical polymerization in $scCO_2$ have been previously described.[4−7]

In contrast, relatively little work appears concerning ring-opening polymerization (ROP) in $scCO_2$.[8−11] Hile and co-workers were the first to report the synthesis of poly(D,L-lactide-*co*-glycolide) (PLGA) in $scCO_2$ in the presence of a stabilizer, poly(perfluorooctyl acrylate).[13] While an increase in yield in the presence of the stabilizer was reported, there was no reported effect on the morphology of the final product. Both of the monomers, D,L-lactide and glycolide, were reported to be largely insoluble in $scCO_2$ under the conditions described, and the precise nature of the polymerization was thought to be an emulsion polymerization. In conventional solvent systems there are a few reports of the use of stabilizers. Dispersion polymerization of L-lactide in conventional hydrocarbon solvents, where the monomer is initially soluble in the continuous phase, has been achieved. Sosnowski and co-workers[14] employed poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) as a stabilizer and obtained well-defined microparticles of PLLA.

An alternative heterogeneous polymerization technique is suspension polymerization, where monomer, polymer and initiator are insoluble in the continuous phase. Suspension polymerization can yield spherical particles in cases where the polymer is soluble in the monomer (known as bead suspension polymerization, i.e., polymerization of styrene) or irregular shapes in cases where the polymer is insoluble in its monomer (known as powder suspension polymerization, i.e., polymerization of PVC).[15] A stabilizer is often added to prevent aggregation of the particles during synthesis. Nieuwenhuis[16] reported the unstabilized suspension polymerization of L-lactide in gasoline, forming a high quality polymer product with an undefined particulate morphology. However, large quantities of organic solvents were used and this is a potential disadvantage for a material destined for biomedical applications.

Scheme 1. Synthesis of PCL−PFPE−PCL



Suspension polymerization is rare in $scCO_2$, due to the high solubility exhibited by most monomers. Cooper and co-workers[17] reported the free radical polymerization of trimethylolpropane trimethacrylate in the presence of poly(vinyl alcohol) in a $scCO_2/H_2O$ mixture. In this Communication, we report the preparation of a well-defined fluorinated triblock copolymer surfactant for suspension polymerization of poly(L-lactide) (PLLA) in $scCO_2$. A commercially available telechelic dihydroxyl terminated perfluoropolyether (PFPE) central block imparts $scCO_2$ solubility ("CO_2-philic"). The two "polymer-philic" segments of the stabilizer consist of short chains of poly(caprolactone) (PCL) grafted to this macromonomer. These segments were chosen to interact with the PLLA particles to facilitate suspension polymerization in $scCO_2$.

Experimental Section: Synthesis of the $scCO_2$ Soluble PCL—PFPE—PCL Stabilizer. The stabilizer synthesis was adapted from that of Pilati et al.[18] beginning with ROP of ϵ-CL from the terminal hydroxyl groups of the "CO_2-philic" PFPE macromonomer, in accordance with the activated chain end mechanism proposed by Penczek[19] (Scheme 1).

Fluorolink D10 (10 g) was reacted in bulk with ϵ-CL (13.5 mL, 6:1 PFPE:CL molar ratio) at 120 °C for 18 h using $Sn(Oct)_2$ (0.5 mL) catalyst. The terminal dihydroxyl groups of the polymer were then end capped with acetyl chloride, to improve solubility in $scCO_2$[20] and to prevent the stabilizer acting as an initiator during the polymerization of L-lactide. ^{1}H NMR analysis showed that the hydroxyl end groups had fully reacted. SEC analysis of this PCL−PFPE−PCL stabilizer exhibits a single peak, demonstrating no homopolymerization of PCL, and PDI was estimated against polystyrene standards to be 1.27, indicating that propagation was controlled. The ^{1}H NMR spectrum of this compound was recorded in $CDCl_3$ and is shown in Figure 1.

* Corresponding author. E-mail: steve.howdle@nottingham.ac.uk.
[†] University of Nottingham.
[‡] Smith & Nephew Group Research Centre.

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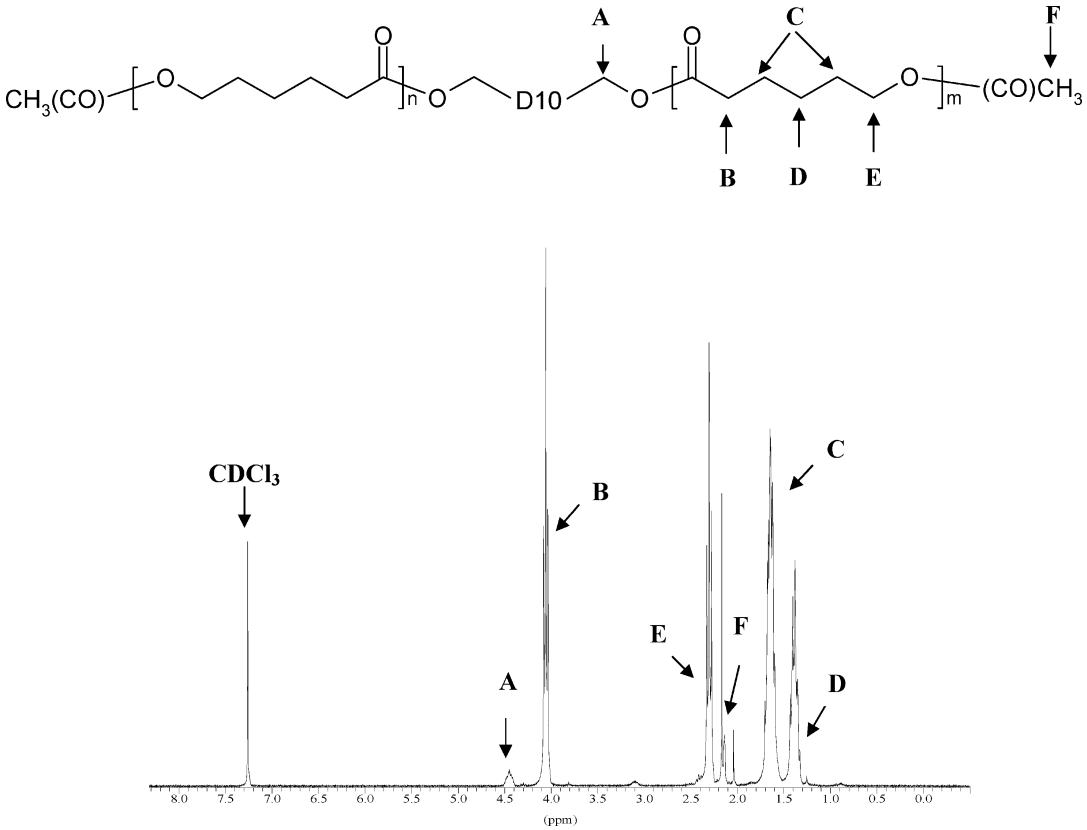

Figure 1. ^{1}H NMR of PCL−PFPE−PCL recorded in $CDCl_3$. Note the key features A and B used to assess the PCL block length.

Integration of the signals from the terminal methylene protons in D10 (A) together with the α-methylene protons on PCL (B) indicates 12 PCL repeat units added to each hydroxyl group. M_n is therefore calculated to be 3200 Da. This is larger than predicted from the feedstock ratio (6:1 ϵ-CL:PFPE), but the use of PFPE diols as macromonomers does result in products of slightly unpredictable composition due to preferential segregation of the catalyst into the ϵ-CL rich phase or the fluorinated phase.[18] Further experimental detail can be found in the Supporting Information.

Suspension Polymerization of L-Lactide in sc-CO_2. ROP was conducted in a 60 mL clamp-sealed autoclave (NWA) equipped with a magnetically coupled overhead paddle bladed stirrer, and a pressure relief valve.[21] Heating was provided via a jacket, monitored by a digital controller (CAL instruments) while the internal temperature was monitored with a thermocouple in contact with the autoclaves contents (RS components). The autoclave was charged with the desired amount of PCL−PFPE−PCL, sealed, and then dried by heating to 130 °C and purging with high grade CO_2 for 1 h before cooling to room temperature. L-Lactide (4 g) was transferred to the autoclave in a glovebag under an argon atmosphere. BuOH (0.05 mL) and $Sn(Oct)_2$ (0.09 mL, $[Sn(Oct)_2]/[BuOH] = 2$, [L-lactide]/[BuOH] = 50) were added into the autoclave using a flame-dried syringe, under a constant positive pressure of CO_2. The autoclave was then pressurized at 80 °C to 3500 psi (241 bar). The overhead stirrer was set to a stirring rate of either 50 or 300 rpm. After 48 h, the autoclave was cooled to room temperature, and slowly vented. The rate of venting was found to have no effect on the morphology of the final product.

Results and Discussion. The solubility of this stabilizer (0.55 g) was examined at 80 °C and 3500 psi in $scCO_2$ using a view cell (90 mL volume) equipped with a sapphire window. The stabilizer was observed to be soluble under these conditions, demonstrating its CO_2-philicity at least up to loadings of 0.006 g/mL, which is equivalent to that used during our polymerization reactions in the 60 mL autoclave. In a similar experiment, L-lactide was found to be insoluble under these conditions, as was $Sn(Oct)_2$. Experiments in the view cell with the stabilizer in the presence of L-lactide revealed two phases, a CO_2-rich phase and a monomer and catalyst mixture. No separate phase was observed for the stabilizer even at loadings of up to 15 wt % (0.01 g/mL), indicating that it is most likely partitioned between the two phases (though it is impossible to determine exactly which phase contains the stabilizer without online sampling).

Table 1. ROP of L-Lactide in $scCO_2$ in the Presence of PCL−PFPE−PCL

entry	% stab[a]	time (h)	stirring rate (rpm)	M_n[b]	PDI[b]	% yield[c]	morphology[d]
A	0	48	300	11 800	1.16	>85	aggregated
B	10	48	300	12 500	1.38	92	fine powder
C	10	48	50	14 500	1.30	88	fine powder
D	10	24	300	11 600	1.14	95	fine powder

[a] w/w with respect to the monomer. [b] Determined by SEC relative to polystyrene. [c] Yield determined gravimetrically, based on mass of polymer obtained after subtraction of the mass of stabilizer added. Note that yield was not accurately determined for sample A, owing to difficulties in removal from the autoclave. [d] Appearance of product directly from autoclave. Each experiment was repeated to demonstrate that the results obtained are readily reproducible and consistent.

This stabilizer was then screened for activity in the ROP of L-lactide in $scCO_2$. In the absence of stabilizer (entry A, Table 1), PLLA is obtained as a hard, white, aggregated solid block. Indeed it is difficult to remove from the autoclave and often requires vigorous physical

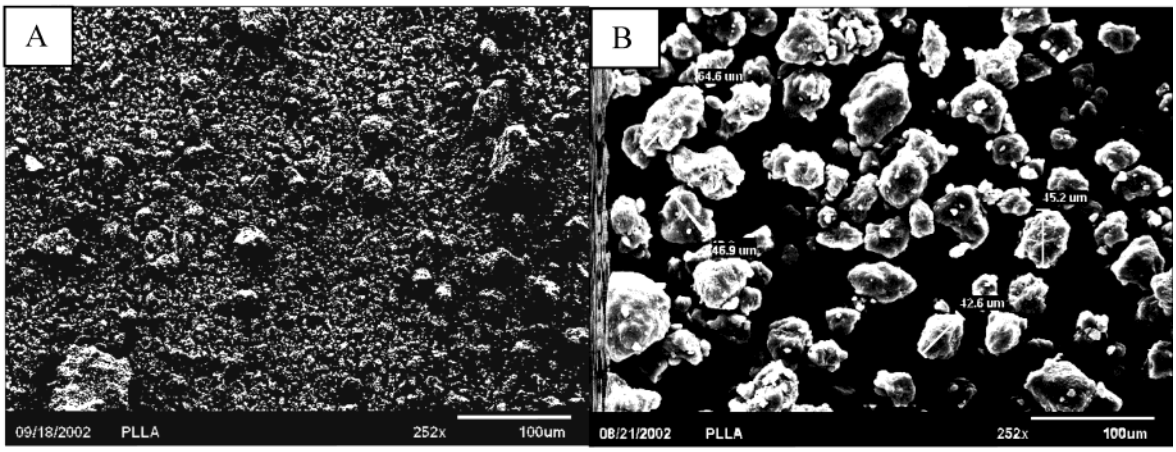

Figure 2. SEM images of PLLA synthesized in $scCO_2$: (A) 10% stabilizer, stirred at 300 rpm; (B) 10% stabilizer, stirred at 50 rpm. The effect of stirring rate can clearly be seen in A and B; note that these are presented on the same scale (100 μm). A minimum of four images were recorded on different areas of each of the samples, and the results here are fully representative of each sample.

activity with a spatula! SEM demonstrates that the sample simply consists of solid PLLA, as is obtained in a conventional bulk synthesis at this temperature. Because of its higher crystallinity and hence melting point,[22] PLLA does not foam after treatment in $scCO_2$, unlike the amorphous poly(D,L-lactide).[23]

In the presence of the PCL−PFPE−PCL (10 wt % with respect to monomer, entry B, Table 1), and under exactly the same conditions, the product is obtained directly from the autoclave as a fine, white powder (Figure 2A) of irregularly shaped particles. This is consistent with a powder suspension polymerization in which the product polymer is not softened by its monomer.[15] The particles show some aggregation, with some larger particles in the size range 40−60 μm but with the bulk of the particles on the order of 5−10 μm.

The particles obtained from suspension polymerizations are very sensitive to the rate of agitation.[15] At a lower stirring rate (50 rpm, entry C in Table 1) there is a very distinct change in morphology demonstrating the expected inverse relationship between stirrer speed and particle size. This sample consists mainly of larger particles on the order of 40−60 μm (Figure 2B). As described earlier, this is typical of suspension polymerization, which involves the direct conversion of monomer droplets into polymer particles.[15] Faster agitation of the mixture results in smaller droplets; hence smaller polymer particles are formed at higher stirring speeds. Further experiments have demonstrated the reproducibility of this process, and we have shown that the stabilizer is active at loadings as low as 5%.

We believe that the PCL−PFPE−PCL anchors to and stabilizes the PLLA after becoming chemically incorporated via transesterification.[24] ^{1}H NMR analysis shows that the stabilizer remains in the product after venting, and most of these residues cannot be removed from the polymer, even via $scCO_2$ extraction. The chemical incorporation of this stabilizer raises certain questions about the toxicity of the PFPE stabilizer. The outer blocks of this stabilizer, PCL, are known to be resorbable and nontoxic.[25] PFPE's are nonresorbable, but are also known for low toxicity,[26] and have been employed in a variety of biomedical applications including oxygen-carrying blood substitutes (Fluosol) and drug delivery systems.[27] The fact that they are not resorbable would clearly be a disadvantage for some applications. Nevertheless, this is the first report of a stabilizer showing good morphological control over the synthesis of a resorbable product in $scCO_2$. We anticipate that this discovery will serve as a "road map" for the synthesis of alternative surfactants for this process.

Table 1 describes the molecular weight characteristics of the PLLA obtained. The molecular weights are higher than one would have predicted from the monomer: initiator ratio, but this is commonly observed with SEC analysis of PLLA against polystyrene standards.[22]

It can be seen that the presence of the stabilizer has no significant effect on molecular weight, indicating that the end capping procedure was successful and that it is not acting as an initiator. Higher PDI is observed in samples reacted for 48 rather than 24 h, indicating the presence of transesterification side reactions that are a common feature of $Sn(Oct)_2$-catalyzed ROP.[25] The low PDI values observed indicate that this suspension synthesis of PLLA in $scCO_2$ occurs in a controlled manner. ^{1}H NMR analysis of the PLLA shows no residual monomer in the product, and none is extracted from the vessel by $scCO_2$; hence, the reaction proceeds to complete conversion in 24 h under these conditions.

Conclusions. A triblock copolymer stabilizer has been synthesized from a commercially available fluorinated PFPE diol. The stabilizer is soluble in $scCO_2$ and effectively stabilizes the ROP of L-lactide in $scCO_2$, leading to the formation of resorbable microparticles in a "one pot" procedure. The molecular weight and yield data are acceptable. As one would predict for suspension polymerization, the stirring rate is important in controlling formation of a fine, powdered product. This is the first time an effective stabilizer has been reported for synthesis of resorbable microparticulate polymers in $scCO_2$.

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Supporting Information Available: Text giving the Experimental Section and a scheme showing the synthesis of

PLLA. This material is available free of charge via the Internet at http://pubs.acs.org.

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